INTRODUCTION

Healthcare improvement has allowed increasingly aggressive management in diagnostic and therapeutic procedures for hematology-oncology patients. These intensified treatments have been associated with severe neutropenia which has been identified as the most important risk factor for infectious complications in patients with neoplastic diseases. As a result, infections become an important cause of morbidity and mortality and are associated with prolonged hospital stay and increased healthcare costs. Therefore, the present study was undertaken to study the incidence of healthcare-associated infections affecting adult patients with leukemia during their admission to Kuwait Cancer Control Center (KCCC). The study also aimed to identify types and microbial etiology of such infections as a step towards improving infection control policies. In addition, testing of antimicrobial susceptibility of isolated Gram-negative bacteria to ciprofloxacin (which is used as oral prophylaxis for gut decontamination during the neutropenia period) was another objective.

SUBJECTS AND METHODS

All adult patients suffering from different types of leukemia who were managed in the Hematology-Oncology unit of Hussein Makki Al-Jumaa Center for Specialized Surgeries (Kuwait Cancer Control Center) over a period of 15 months from January 2006 to March 2007 were enrolled in the present study. Prospective surveillance of healthcare-associated infections was performed based on the Center for Disease Control and Prevention (CDC) standard definitions for nosocomial infections. Healthcare-associated infections were diagnosed by collecting information from clinical data (symptoms and signs).
investigations (laboratory, radiological, etc) and microbiological culture and sensitivity results.

The study was approved by the Ethical Committee of the Ministry of Health. Patients’ clinical data were obtained from charts, doctors’ notes, nurses’ notes, and additional information provided from the attending physicians.

The findings were recorded in a preformed format that included demographic data, specific medical devices used (peripheral or central venous catheters, urinary catheters, nasogastric tubes and endotracheal tubes), WBCs and neutrophil counts and antibiotics used including ciprofloxacin oral prophylaxis. Data about the details of healthcare-associated infection episodes such as date and site of onset, clinical findings, investigation done and microbiologic culture and sensitivity results were included. Antimicrobial susceptibility of the isolated Gram-negative bacteria to ciprofloxacin was performed in Ibn Sina Hospital Laboratory Department.

In cases of blood stream infections (BSI), urinary tract infections (UTI) and pneumonia (PNEU), the infections were specified as device-associated (central line, indwelling urinary catheter and ventilator respectively) or not device-associated. This was in accordance with the CDC / National Healthcare Safety Network (NHSN) patient safety component protocol.

Neutropenic fever of unknown origin that was without evidence of a specific infection at any site and without an identifiable pathogen from body specimens (lacks a direct microbiological or clinical confirmation and may thus be of limited specificity) was excluded from the present study.

Incidence density rate of healthcare-associated infections was calculated by the following formula:

\[
\text{Incidence density rate of healthcare-associated infections} = \frac{\text{Number of new nosocomial infections acquired in the study period} \times 1000}{\text{Total of patient-days for the study period}}
\]

**Statistical methodology**

Data were collected and then entered into the computer using the SPSS version 12 for Windows. Entered data were checked for accuracy and then for normality. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as mean (\(X\)) and standard deviation (S).

The following statistical tests were used:

1. Independent samples t-test was used as a parametric test of significance for comparison between two sample means.
2. The \(X^2\) test was used as a test of significance for comparison between the incidence density rates.
3. The Fisher’s exact test was used whenever the \(X^2\)-test was not appropriate.

A 5% level was chosen as a level of significance in all statistical significance tests used.

**RESULTS**

The study included 245 adult patients with different types of leukemia. Their ages ranged from 18-78 years with mean of 42.19 ± 14.51 years. There were 163 (66.5%) male and 82 (33.5%) female patients. The patients stayed 8445 days in KCCC during the study period. The majority of patients (53.9%) were suffering from acute myelocytic leukemia (AML) (Table 1).

The study revealed that a total of 113 healthcare-associated infections developed in 73 patients. Their ages ranged from 18-74 years with a mean of 40.01 ± 12.59 years. Forty-two (57.5%) were female whereas 31 (42.5%) were male.

The age difference between the patients who developed infections and patients who did not was not statistically significant (t = 1.535, p = 0.126). However, the sex difference was significant (\(X^2 = 27.043, p < 0.001\)) and female patients were more prone to infections.

<table>
<thead>
<tr>
<th>Type of leukemia</th>
<th>Patients (n, %)</th>
<th>Number of infections</th>
<th>Number of patient days</th>
<th>Incidence density rate of healthcare-associated infections /1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myelocytic leukemia (AML)</td>
<td>132 (53.9)</td>
<td>70</td>
<td>4315</td>
<td>16.2</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia (ALL)</td>
<td>58 (23.7)</td>
<td>41</td>
<td>3122</td>
<td>13.1</td>
</tr>
<tr>
<td>Chronic myelocytic leukemia (CML)</td>
<td>35 (14.3)</td>
<td>2</td>
<td>680</td>
<td>2.9</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>20 (8.1)</td>
<td>0</td>
<td>328</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>245 (100)</td>
<td>113</td>
<td>8445</td>
<td>13.4</td>
</tr>
</tbody>
</table>

*Table 1: Distribution of adult patients with leukemia according to the disease type and incidence rate of healthcare-associated infections*
The overall incidence density rate of healthcare-associated infections was 13.4 / 1000 patient days. The rates were significantly higher in acute types of leukemia than chronic ones ($X^2 = 11.261, p = 0.001$). AML had the highest infection rate (16.2 / 1000 patient days).

The most frequently reported infections were blood stream infections (BSI, 46.9%) followed by skin and soft tissue infections (SST, 25.7%). Pneumonia (PNEU) represented 11.5% while urinary tract infections (UTI) represented 7.1% of the total infections. Oral candida mucositis was reported in 2.7% of cases. Clostridium difficile (C. difficile) accounted for 1.7% and 4.4% constituted other infections.

Seventy nine infections (69.9%) were due to Gram-negative bacteria while 21 (18.6%) and five (4.4%) infections were due to Gram-positive organisms and fungi respectively. Eight infections clinically diagnosed without microbiological documentation represented 7.1% of all infections; half of them were pneumonia cases. Escherichia coli (E. coli) were isolated from the majority of microbiologically documented infections (35.2%). Pseudomonas aeruginosa (P. aeruginosa) was the second commonest encountered pathogen causing 16 (15.2%) of microbiologically proven infections. The distribution of the different pathogens among the different types of healthcare-associated infections is shown in Table 2. Only 22 infections (19.5%) were associated with a neutrophil count > 1000 cell/mm$^3$ while 91 infections (80.5%) were associated with neutrophil count of < 500 cell / mm$^3$ in patients receiving ciprofloxacin prophylaxis.

The majority of isolated Gram-negative bacteria were ciprofloxacin resistant. All E. coli isolates from different types of infections were ciprofloxacin resistant except one strain (overall resistance 97.3%).

### Table 2: Pathogens causing healthcare-associated infections in adult leukemia patients from January 2006 -March 2007 at KCCC

<table>
<thead>
<tr>
<th>Organism</th>
<th>UTI</th>
<th>PNEU</th>
<th>GI</th>
<th>ORAL</th>
<th>BSI</th>
<th>SST</th>
<th>others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Methicillin -resistant Staphylococcus aureus</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase -negative staphylococci</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus gallinarum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td>22</td>
<td>10</td>
<td>37</td>
<td></td>
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<tr>
<td>Enterobacter cloacae</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteus mirabilis</td>
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<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Stenotrophomonas maltophilia</td>
<td>3</td>
<td>5</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Chryseobacterium. meningosepticum</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Burkholderia cepacia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Candida krusei</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Culture not done</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No pathogen isolated</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>13</td>
<td>2</td>
<td>3</td>
<td>53</td>
<td>29</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

UTI = urinary tract infection; PNEU = pneumonia; GI = gastrointestinal system infection; BSI = blood stream infection; SST = skin and soft tissue infection; Others: $surgical site infection (SSI), *Hickman exit site infection, +sinusitis
which was isolated from SST infection. Four isolates (57.1%) of Klebsiella pneumoniae (K. pneumoniae) were resistant to ciprofloxacin. E.coli were significantly more resistant to ciprofloxacin than K. pneumoniae (p = 0.01). The susceptibilities of the isolated Gram-negative bacteria to ciprofloxacin are shown in Fig. 1.

Out of BSI, 44 infections (83%) were central line-associated. Regarding UTI, four infections (50%) were associated with indwelling urinary catheter while no case was diagnosed as ventilator associated pneumonia (VAP).

DISCUSSION

The increasingly intensified chemotherapy in hematology-oncology population have led to higher hematologic toxicity with more severe and prolonged neutropenia, as well as other types of immunosuppression, making these patients more vulnerable to nosocomial infections[9]. Our results revealed that the overall incidence of healthcare-associated infections in adult patients with leukemia was 13.4 / 1000 patient days. Higher incidence (17.7 / 1000 patient days) was reported by Urrea et al[9] in pediatrics with different hemato-oncology diseases and not only confined to leukemia as in our study. Moreover, in their study, they did not perform intestinal decontamination in neutropenic patients. On the other hand, our patients received ciprofloxacin (for gut decontamination) with or without antifungal prophylaxis during the neutropenia period (ANC < 1000 c/mm³). Engelhart et al[10] reported a lower incidence (11 / 1000 patient days) of nosocomial infections among adults with different hematology-oncology diseases and not only leukemia.

In the present study, the incidence density rates were significantly higher in acute types of leukemia than in chronic ones. Several studies reported that patients with acute leukemias are more prone to infection complications. This marked susceptibility generally results from both chemotherapy-induced neutropenia, which is typically prolonged and profound, and mucositis affecting the oropharynx and gastrointestinal tract[10-14].

Female patients significantly developed more infections in the present study; however, we could not find any reports in the literature regarding sex difference in the susceptibility of adult leukemia patients to infections.

Several studies indicate that at least half of neutropenic patients who have a fever of unknown origin have an established or occult infection[10,11]. However, fever can also be a manifestation of many non-infectious causes such as the underlying leukemia, transfusion reactions, thrombo-embolism, drugs, allergic reactions, hematomas and radiation injury[10,11]. The proportion of non-infectious causes of fever of unknown origin can be reduced further by a thorough clinical assessment[12].

The appearance of fever in a neutropenic patient is considered a medical emergency and requires immediate attention[13]. Due to the severity and high mortality of infections in this patient population, prompt empiric therapy is mandatory. Therefore, for many febrile episodes, the infectious etiology cannot be established before antimicrobial therapy is initiated[14]. Diagnosis of infections in neutropenic patients is often impeded, because a marked decrease in the number of neutrophils is associated with a diminished
inflammatory response and often muted clinical signs\textsuperscript{[12]}. Drug fever can occur after the administration of virtually any medication, even one administered for long periods without problems\textsuperscript{[13]}. Based on the previous facts and due to lack of microbiological or clinical confirmation and limited specificity of fever of unknown origin, we excluded this clinical entity from the present study.

In the present investigation, 80.5% of infections developed during the period of severe neutropenia (neutrophil count of < 500 cell/mm\textsuperscript{3}). Several studies stated that, patients with severe neutropenia are at high risk for bacterial and fungal infections\textsuperscript{[6-10,15,16]}. The organisms responsible for infections associated with neutropenia are most often the patient’s own bacteria\textsuperscript{[13]}. The primary source of pathogens is the alimentary tract, where cancer chemotherapy-induced mucosal damage allows invasion of endogenous organisms. Similarly, skin damaged by invasive procedures, \textit{e.g.}, with vascular access devices, is another portal of entry for infectious organisms\textsuperscript{[13]}.

In addition to exogenous routes of infection, the endogenous intestinal bacterial flora is a potential source of life-threatening bacteremia caused by Gram-negative microorganisms, with intestinal colonization being the antecedent to bacterial translocation across the gut and systemic dissemination. To reduce the incidence of bacteremia, such patients often receive antibiotic prophylaxis, called selective decontamination of the gut. This prophylaxis is intended to eliminate potentially pathogenic bacterial species while maintaining native anaerobic flora. The fluoroquinolones such as ciprofloxacin show excellent activity, good bioavailability, and high concentrations in the gut, and thus provide an important component of the standard selective decontamination in many centers including our center\textsuperscript{[17-20]}. As a result of this practice, during the past two decades, the microbial etiology of BSI in patients with febrile neutropenia has shifted from Gram-negative to Gram-positive organisms in many centers\textsuperscript{[6,11,13]}.

In the present study, despite the use of ciprofloxacin prophylaxis for acute leukemia patients during neutropenic period (ANC < 1000 c/mm\textsuperscript{3}), the most frequently reported infections were primary BSI caused by Gram-negative bacteria, predominantly \textit{E. coli}, which were all resistant to ciprofloxacin. Similarly, Gomez et al\textsuperscript{[21]} reported higher rate of Gram-negative bacteremia in the ciprofloxacin receiving group than in the control group not receiving prophylaxis. Their study was carried out among adult patients with acute leukemia who developed episodes of febrile neutropenia. Cattaneo \textit{et al}\textsuperscript{[22]} in their study on infections in patients with hematological malignancy used levofloxacin prophylaxis in patients with more than seven days expected neutropenia. They reported that Gram-negative (49.4\%) outweighed Gram-positive bacteria (40.9\%), \textit{E. coli} being most frequent (23.2\%) and 86.8\% of \textit{E. coli} were quinolone resistant. Uqarte -Torres \textit{et al}\textsuperscript{[23]} reported that bacteremia was most frequently caused by Gram-negative organisms (18 / 29), \textit{E. coli} being the most commonly isolated pathogen in their study on leukemia patients.

Central venous catheters (CVCs) are necessary to facilitate treatment of hematologic disorders, but catheter-related bloodstream infections (CR-BSIs) are important causes of morbidity and mortality, and may lead to interruptions in planned therapy for malignancy or increases in length of hospital stay\textsuperscript{[24]}. In the present study, 83\% BSIs were associated with a central line. Inorder to determine that central venous catheters were the source of bloodstream infections (central line related BSI), specific criteria including the requirement of peripheral blood cultures and catheter-tip cultures to be positive, together with other methods of confirmation. Confirmatory microbiological methods include a differential time to positivity of > 2 hours (blood culture drawn from the catheter becomes positive at least two hours earlier than a simultaneously drawn peripheral blood culture) and a > 5:1 ratio of simultaneously drawn quantitative central blood culture compared with peripheral blood culture\textsuperscript{[24, 25]}. These criteria were not implemented in our center.

Skin and soft tissue infections represented about one quarter of infections in leukemic patients in the present study. They are mainly caused by \textit{E. coli} and \textit{Paeruginosa}. SST represented 13\% of infections in patients with acute leukemia reported by Jagarlamudi \textit{et al}\textsuperscript{[26]}, Lopez and Sanders\textsuperscript{[27]} stated that \textit{P. aeruginosa} has an important role in SST infections in febrile neutropenic patients with cancer. Prevention in immuno-compromised patients is important and demands careful attention to measures that protect the skin from unnecessary trauma, maceration, or alterations in the normal microbial flora\textsuperscript{[28]}.

In the present investigation, culture of specimens from the respiratory tract of patients with clinical and radiological evidence of pneumonia was unrevealing in 30.8\% of cases. Madani\textsuperscript{[29]} stated that the majority of pneumonia cases in his study on acute AML patients were culture negative. Engelhart \textit{et al}\textsuperscript{[10]} isolated pathogens from only one third of pneumonia cases. Negative cultures may be due to either early antibiotic administration or inadequate specimens submitted for microbiologic evaluation\textsuperscript{[29]}.

**CONCLUSION**

Despite the use of prophylactic antibiotics, infections remain a major complication in adults with acute leukemia. Infection is directly proportional to the degree of neutropenia. Continuous monitoring of the rate of Gram-negative bacteremia is recommended for timely detection of the loss of efficacy of fluoroquinolone prophylaxis.
We expect that these data will guide local prevention strategies and could help to design control guidelines aimed at reducing infection rates, morbidity and mortality associated with infections in leukemic patients.

ACKNOWLEDGEMENT
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REFERENCES